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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/954,771	10/20/1997	PHILIP w INGham	HMSU-P11-006	6520
28120	7590	07/10/2002		
ROPS & GRAY ONE INTERNATIONAL PLACE BOSTON, MA 02110-2624			EXAMINER	
			BRANNOCK, MICHAEL T	
			ART UNIT	PAPER NUMBER
			1646	301
DATE MAILED: 07/10/2002				

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No. 08/954,771	Applicant(s) Ingham, PW
	Examiner Michael Brannock, Ph.D	Art Unit 1646

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Attachment to Advisory Action

1. Claims 123-165 stand provisionally rejected under the judicially created doctrine of double patenting over claims 11-13 of copending Application No. 08/462386. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: *in vitro* methods of promoting the growth, differentiation and/or survival of neuronal cells by contacting the cells with a sonic hedgehog protein.

Applicant's intention (Paper 28) to provide a terminal disclaimer is acknowledged.

Claim Rejections - 35 USC § 112

2. The rejection of claims 132 and 154 under 35 U.S.C. 112, second paragraph, as set forth in item 9 of Paper 36 is withdrawn in view of Applicants' amendments put forth in Paper 38.
3. Claims 123-165 stand rejected under 35 U.S.C. 112, first paragraph, as set forth previously in item 12 of Paper 36 and in item 13 of Paper 26, because the specification, while being enabling for methods of promoting growth, differentiation and/or survival of embryonic neuronal cells by administering a polypeptide (sonic hedgehog) of SEQ ID NO: 8, 11, 12, and 13

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or an N-terminal autoproteolytic portion thereof (as described in the specification), does not reasonably provide enablement for administering a polypeptide other than a polypeptide of SEQ ID NO: 8, 11, 12, and 13, nor for the administration of portions of the polypeptides other than that of the N-terminal autoproteolytic portion, and nor does the specification provide enablement for promoting growth, differentiation and/or survival of neuronal cells other than embryonic cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the reasons of record.

Applicant argues that it would not take undue experimentation to determine that hedgehog proteins function in the adult nervous system. Applicant's arguments regarding the use of hedgehog polypeptides in the adult nervous system have been substantially addressed previously. Applicant additionally argues that one of skilled in the art would not be dissuaded from trying to find a way to use the hedgehog polypeptides in the adult because of the teachings in the specification that were pointed to by the examiner, e.g. that hedgehog proteins were known in the art to work only in embryonic tissue and that the specification indicated that hedgehog protein were not expressed in adult tissues. Rather, Applicant asserts that the artisan would be concerned only with the expression of the hedgehog receptor *patched* in the adult. This argument has been fully considered but not deemed persuasive. As set forth previously, the specification discloses experiments that indicate sonic hedgehog is not expressed in adult tissues (see page 110, lines 10-11). One of skill in the art would therefore expect that adult tissues would not be

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responsive to sonic hedgehog in the same way that embryonic tissues are, or perhaps not responsive at all. The specification has provided no guidance as to the nature of the response of adult tissues to sonic hedgehog. Additionally, Applicant essentially admits that the specification does provide any information about patched expression in the adult either. Applicant, provides a pre-filing date reference (Takabatake et al., FEBS Letts 410(485-489)1997) that indicates that Shh and patched are expressed in in adult neural ocular tissues and other adult tissues.

Takabatake et al., merely speculate that "judging from their roles in embryos, hh molecules might function in certain cell-cell communications between deferent types of tissues in the adult eye" (see col 1 of page 489). Other - post filing date references, referred to by Applicant, provide more information as to potential roles of hh proteins in the adult, however, as set forth previously, it this type of research and investigation that would need to be performed, e.g. to find neural tissues in the adult, that needs to be performed before the skilled artisan can use the hedgehog polypeptides as claimed. The instant specification ,as well as the prior art at the time of filing, provide only speculations and an invitation to perform this type of research.

Applicant's arguments regarding enablement of methods using amino acid sequence variants of hedgehog polypeptides have been substantially addressed previously. Additionally, Applicant argues that techniques in combinatorial chemistry, etc., have trivialized the construction and screening of protein variants. This argument has been fully considered but not deemed persuasive. The references cited by Applicant regarding combinatorial mutagenesis are each directed to prokaryotic proteins expressed in bacteria wherein a rapid assay system for each

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has been well developed in the art. There is no indication, either in the specification nor in the prior art, that the techniques now referred to by Applicant are amenable to use with the proteins encompassed by the instant invention, wherein assays involve integral membrane proteins and/or nervous tissue.

Additionally, the rejection is not based on a lack of understanding as to why the invention works, as alleged by Applicant. The rejection is based on the fact that the specification has failed to provide sufficient guidance to use hedgehog proteins for the growth or promotion of survival of any particular adult nervous tissue, nor how to make variants of hedgehog proteins to be used with embryonic tissue without undue experimentation on the part of one highly skilled in the art.

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Conclusion

No claims are allowable.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Fridays from 8:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

July 2, 2002

Yvonne Eyler
YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
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